REMARKS

Applicants appreciate the Examiner's withdrawal of the previous rejections. In response to the objections and rejections presented in this Office Action, Applicants have amended the specification and the claims. Reconsideration of objections and rejections is respectfully requested in view of the above amendments and the following remarks.

I. Amendment to the Specification

The specification was amended to include the continuity data of the application. No new matter is introduced.

II. Amendment to the Claims

Claims 1 and 27 are amended to include the limitation from the original claim 3, reciting the amino acid range "70 to 84" of SEQ ID NO: 2. Claims 1 and 27 are also amended to clarify the steps of the methods, respectively, and to recite the Markush language as the Examiner suggested. Claim 3 is cancelled. Claim 4 is amended to clarify "the quantifying" as "the quantifying step (c)." Claim 28 is amended to recite "hepcidin" and "or fragments thereof" to distinguish from claim 30. Support is found throughout the specification, at least in the original claim 15. Claim 29 is cancelled. Claims 15, 25 and 30 are corrected for formality.

Accordingly, no new matter is introduced in this amendment.

III. Status of the Claims

Claims 1, 4, 15, 25, 27, 28, and 30 are amended. Claims 2-3, 5-14, 17-24, and 29 are cancelled. Upon entry of this amendment, claims 1, 4, 15-16, 25-28, and 30 are pending in this application.

IV. The Invention

The instant invention is drawn, in one aspect, to a method for diagnosing a condition of a disease characterized by non-physiological levels of hepcidin, comprising the steps of: (a) obtaining a tissue or fluid sample from a subject; (b) contacting the sample with an antibody or fragment thereof that specifically binds to one or more carboxy terminal epitopes of SEQ ID NO: 2; and (c) quantifying hepcidin level in the sample; wherein the disease is selected from chronic renal insufficiency, renal anemia and hereditary hemochromatosis; the tissue or fluid sample is selected from kidney samples, liver samples, and urine samples; and the non-physiological level of hepcidin is indicative of the disease.

V. Argument

A. Objection to the Specification

The Examiner objected to the specification for the informalities on page 1 that are related to the current status of the non-provisional applications to which this application is related to. Thus, Applicants have amended the first paragraph of the specification as the Examiner suggested, by incorporating the patent numbers of the parent application. Moreover, the amendment also includes the parent PCT application to which this application claims priority benefits. Support is found in the prosecution history of this application, for example, the Filing Receipt mailed on September 18, 2006.

B. Rejections based on 35 U.S.C. § 112, second paragraph (indefiniteness)

The Examiner rejected claims 1, 3, 4, 15, 16, and 25-30 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Specifically, the Examiner rejected claim 1 as reciting improper Markush language in lines 6 and 11. (Office Action, page 3). Although Applicants maintain that the phrases "the disease is selected from" and "the tissue or fluid sample is selected from" are proper to recite the Markush groups and they impart the same meanings as the formal Markush language suggested by the Examiner, Applicants have amended the claim reciting the language as the Examiner suggested.

Moreover, the Examiner asserted that claim 1 is incomplete allegedly because the claim fails to clearly define what non-physiological level is expected to be obtained so as to be correlated to indication of a disease characterized by non-physiological levels as required by the preamble. (Office Action, page 3). Applicants respectfully disagree.

The instant invention is directed, inter alia, to a method of diagnosing a disease by measuring the level of hepcidin in a tissue or fluid sample of a subject and comparing the same with the normal level of hepcidin in a corresponding sample in a healthy subject. For each subject, different diseases, or different types of samples, may have different characteristic "physiological levels" of hepcidin; therefore, it would not be practical or meaningful to list the "non-physiological levels" of hepcidin for every disease concerned.

More importantly, a person of ordinary skill in the art, i.e., a clinician familiar with the characteristics of a particular disease, would be able to use the value of hepcidin level obtained to assess the possibility of whether a patient has likely been inflicted with the particular disease.

Thus, Applicants respectfully submit that the non-physiological level of hepcidin is not necessary, and in fact not relevant, to the patentability of the claims.

C. Rejections based on 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejected essentially all the claims under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement for various reasons. Applicants respectfully traverse.

(1) Rejection of claims 1, 3, 4, 15, 16, and 25-30

The Examiner rejected claims 1, 3, 4, 15, 16, and 25-30 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleged that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserted: "The application does not disclose an antibody which specifically binds to any carboxy terminal portion of hepcidin in SEQ ID NO 2. The only C-terminal antibody of hepcidin disclosed in the specification is specific for epitopes within amino acids 70-84 of SEQ ID NO 2." Applicants respectfully submit that the two assertions are contradictory to each other and that the rejection is in error as a result of confusion between the written description requirement and enablement requirement.

"An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." M.P.E.P. § 2163(I) (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." M.P.E.P. § 2163(I) (citing *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the*

University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)).

In this application Applicants have described the claimed invention "with all of its limitations using such descriptive means as words, structures, figures," e.g., Figures 1-14 and paragraphs and specification from page 12 through page 91, which "fully set forth the claimed invention." These figures and descriptions have provided adequate characteristics to show that Applicants were in possession of the claimed invention at the time the application was filed.

As Applicants have pointed out previously, the invention has been described in terms of:

> (a) generating a hepcidin protein, including prohepcidin or fragments thereof; (b) generating antibodies that specifically bind a hepcidin protein, including prohepcidin or fragments thereof; (c) diagnostic assays and kits for diagnosing subtyping or monitoring the diseases described herein; (d) methods for over expressing and down regulating hepcidin or prohepcidin; and (e) therapeutic treatment of the diseases described herein.

(Specification, page 12, lines 16-23.) Although the Examiner has impliedly argued that the description does not provide information on actual reduction to practice in all aspects of the invention, the Examiner's argument does not justify a rejection of the claims, because written description requirement does not demand actual reduction to practice for all embodiments and all aspects of the invention. To say the least, Applicants have provided information on actual reduction to practice in some aspects, for example, as the Examiner has acknowledged, the disclosure that "the C-terminus antibody EG(1)-HepC is raised against amino acids 70-84," and constructive reduction to practice in other aspects, for example, again as the Examiner has acknowledged, the disclosure of "the C-terminus of hepcidin as being amino acids 65 to 84."

Moreover, the Examiner cited Swinklers et al., (*Clinical Chemistry* 52(6), 950-968 (2006)) and Kemna et al. (*Haematological* 93(1), 90-97 (2008)) to show the difficulties in the production of specific anti-hepcidin antibodies due to the small size of hepcidin and the compact and complex structure of the molecule; however, these references are irrelevant to the written description requirement under 35 U.S.C. § 112, first paragraph.

Applicants respectfully submit that the citation of these references is a result of confusion between the written description requirement and the enablement requirement by the Examiner. The written description requirement "is separate and distinct from the enablement requirement."

M.P.E.P. § 2163(I) (citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991)). In fact, the citation of Swinklers et al. and Kemna et al. by the Examiner is a testimony of the significance, thus patentability, of the instant invention. The difficulties encountered by Swinklers et al. and Kemna et al., or others cited by these two references, are exactly the ones Applicants sought to overcome and have indeed overcome, i.e., identifying the antibodies despite the small sizes of hepcidin.

(2) Rejection of claims 1, 3, 4, 15, 16, 25, and 26

The Examiner also rejected claims 1, 3, 4, 15, 16, 25, and 26 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement, based on the assertion that "the specification does not show that the antibodies thereof bind or is reactive specifically to the carboxy terminal epitopes of SEQ ID NO: 2 that render it diagnostic for chronic renal insufficiency, renal anemia, and hereditary hemochromatosis." (Office Action, pages 5-6).

The Examiner's rejection is in error for various reasons. First, the disclosure of the instant application has provided sufficient support for the claims. As the Examiner has acknowledged, "[t]he specification (e.g. p. 11, lines 25-27, pgs. 49-50) teaches and shows blood samples and ELISA assays using N-terminal antibodies to hepcidin to show a correlation with chronic renal insufficiency, renal anemia and hereditary hemochromatosis," and "[t]he specification also provides that the C-terminal antibody EG(1)-hepC binds to hepcidin in western blot, immunochemistry and immunofluorescence assays(e.g. p. 6 and p. 55)." (Office Action, page 5). Moreover, as the Examiner has also acknowledged, the present application has disclosed that the C-terminal antibody EG(1)-HepC is raised against amino acids 70-84. (See Office Action, page 4). These disclosures should be sufficient to support the claimed subject matter, i.e., a method for diagnosing a disease characterized by non-physiological levels of hepcidin, such as chronic renal insufficiency, renal anemia, and hereditary hemochromatosis, by contacting a tissue or fluid sample from a suspected patient with an antibody or fragment that specifically binds to one or more carboxy terminal epitopes of SEQ ID NO: 2 and quantifying the hepcidin level in the sample.

Second, the Examiner's assertion is an unjustifiably narrow interpretation of the disclosure presented. The Examiner appears to imply that the application has not provided evidence that binding of antibodies or fragments thereof would bind or react specifically enough to the carboxy terminal epitopes of SEQ ID NO: 2 to render the diagnosing method unique in

determining whether a specific disease exists. However, the claims do not contain such language as to limit the method to that which by itself would be determinative of whether a disease exists. Instead, this invention is intended to provide a clinician with a new tool in diagnosing diseases. It should be apparent to a person of ordinary skill in the art that the present invention would constitute a useful tool complementary to other existing tools in diagnosing the diseases related to the hepcidin activity.

Moreover, the claims, at least as amended, have adequate support because, as the Examiner has acknowledged, the specific binding of antibody or fragment thereof with the one or more C-terminal epitopes contained within amino acids 70 to 84 of SEQ ID NO: 2 has been disclosed in numerous places in the specification.

Therefore, Applicants respectfully request that the rejection of claims based on written description requirement under 35 U.S.C. § 112, first paragraph, be withdrawn.

D. Rejections based on 35 U.S.C. § 112, first paragraph (enablement)

The Examiner rejected all the claims as not meeting enablement requirement under 35 U.S.C. § 112, first paragraph, for various reasons. Applicants respectfully traverse.

(1) Rejection of claims 1, 3, 4, 15, 16, and 25-30

The Examiner rejected claims 1, 3, 4, 15, 16, and 25-30 as allegedly not enabling under 35 U.S.C. § 112, first paragraph. The Examiner asserted that "[t]he specification fails to teach a method of detecting hepcidin with an antibody which specifically binds to any carboxy terminal portion of hepcidin." (Office Action, page 7). The Examiner made the assertion despite the acknowledgment that "[t]he specification on page 4 discloses the C-terminus of hepcidin as being amino acids 65 to 84," and that "[t]he specification on page 6 discloses the C-terminal antibody EG(1)-HepC is raised against amino acids 70-84." *Id.* While acknowledging that the disclosure is enabling for detecting hepcidin with an antibody or fragment thereof that specifically binds to one or more epitopes of hepcidin located with amino acids 70-84 of SEQ ID NO: 2, the Examiner also contradictorily asserted that the disclosure is not enabling for "any and all carboxy terminal epitopes of SEQ ID NO 2 as broadly recited." (Office Action, page 6). Applicants respectfully submit that the Examiner erred in misapplying the enablement requirement to this application.

"The enablement requirement refers to the requirement of 35 U.S.C. 112, first paragraph that the specification describe how to make and how to use the invention." M.P.E.P. § 2164.

"However, to comply with 35 U.S.C. 112, first paragraph, it is not necessary to 'enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.'" M.P.E.P. 2164 (citing *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) (holding that an invention directed to a general system to improve the cleaning process for semiconductor wafers was enabled by a disclosure showing improvements in the overall system)(emphasis added).

"A single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled." M.P.E.P. § 2164.02. "The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors." *Id.* (emphasis added). "To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." *Id.* In this case, as the Examiner has acknowledged, the disclosure contains at least one functional working example. In the meantime, the specification also provides clear guidance on similar working examples in precise terms.

In the Office Action, although the Examiner has cited the factors listed in *In re Wand*, the Examiner has failed to consider them either specifically or collectively. In fact, even in *In re Wand* itself, the Court held that the specification was enabling because "there was considerable direction and guidance" in the specification, there was "a high level of skill in the art at the time the application was filed," and "all of the methods needed to practice the invention were well known." *In re Wands*, 858 F.2d 731, 740, 8 USPQ2d 1400, 1406 (Fed. Cir. 1988).

Here, likewise, the disclosure has provided considerable direction and guidance on how to use the invention, there was a high level of skill in the art, and all of the methods needed to practice the invention were well known, i.e., taking fluid sample from a patient, contacting the sample with an antibody that specifically binds to certain portion(s) of the hepcidin, and measuring the hepcidin level in the sample to compare with the normal level of hepcidin.

Third, the Examiner's argument that one working example is not sufficient to support the breadth of the claims is also misplaced. Given the disclosure of the EG(1)-HepC antibody that can specifically bind to epitopes within amino acids 70-84 of SEQ ID NO 2 and the detailed procedure on how to use it, the use of other antibodies would be similar.

It has been long established that "[a]n applicant need not have actually reduced the invention to practice prior to filing." M.P.E.P. 2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), holding that "[t]he mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956))).

Moreover, the Examiner's attention is drawn to the fact that Applicants have solved the problems due to the small size of the hepcidin protein faced by other researchers such as Winklers et al. and Kemna et al. Applicants have successfully used an antibody to bind an even smaller amino acid portion of the hepcidin, i.e., amino acids 70-84 of SEQ ID NO: 2. Applicants cannot see the logic by which the Examiner is rejecting an advanced technology based on the failed attempts by other researchers in the relevant art. As has been discussed above, the very references cited by the Examiner should foster the patentability of the instant invention, not the other way around.

Thus, this ground of rejection should be withdrawn, at least in light of the new amendment presented herein.

(2) Rejection of claims 1, 3, 4, 15, 16, 25, and 26

The Examiner rejected claims 1, 3, 4, 15, 16, 25, and 26 based on the enablement requirement under 35 U.S.C. § 112, first paragraph, mainly based upon the following assertions: (1) the claims do not include the specific range of non-physiological level of hepcidin; (2) the specification does not provide graphs or statistical values which provide a correlation of hepcidin levels compared to standards or control; (3) the only examples for detecting prohepcidin in human were directed to a sensitive ELISA, but the C-terminal antibody EG(1)-HepC showed no immunoreactivity in this ELISA assay (Office Action, page 10); and (4) the specification does not enable one skilled in the art to positively diagnose the diseases as claimed because of lack of knowledge on physiological levels of hepcidin.

Applicants respectfully note that the enablement requirement should be viewed from the position of one of ordinary skill in the art (MPEP § 2164.01(a)) and in this field, the ordinary skill is undeniably high. Accordingly, a person of ordinary skill would be capable of making reasonable correlations between the disease recited in the previously submitted articles and hepcidin levels. As Applicants have respectfully drawn the Examiner's attention to in the

response to the previous office action on the similar enablement issue, "[t]he evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." MPEP § 2164.05 (emphasis added). A diagnostic test is any kind of medical test performed to aid in the diagnosis or detection of disease. "Clinicians use laboratory tests to help them make choices. Test results may help reduce uncertainty, make a diagnosis (diagnostic testing), or identify patients who are likely to have occult disease (screening)." (Merck Manuals Online Medical Library, http://www.merck.com/mmpe/print/sec22/ch328/ch328d.html.) (last visited July 9, 2009).

In this application, Applicants respectfully submit that the evidence on how to practice the claimed invention can convince a person of ordinary skill in the art that the diagnostic method would work to aid a clinician to determine whether the disease is present. Even if the diagnostic method by itself would not be determinative, Applicants respectfully submit that the diagnostic method as claimed can well serve the purpose of aiding a clinician in determining whether a disease associated with the activity of hepcidin protein is likely or unlikely present.

While maintaining that the methods are enabling within the full scope of the claims, for the sole purpose of advancing the prosecution of the application, Applicants have amended claims 1 and 27 without prejudice to recite the amino acid range 70 to 84 of SEQ ID: 2 to which the antibody or fragment specifically binds to. As has been acknowledged by the Examiner, this working example has been disclosed specifically in this application.

Accordingly, in view of the amendments and arguments above, Applicants respectfully request the Examiner to withdraw the rejections on the enablement ground under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants believe that this application is in a condition for allowance and an early notice to this effect is earnestly solicited. If the Examiner does not believe that such action can be taken at this time or if the Examiner feels that a telephone interview is necessary or desirable, Applicants welcome the Examiner to call the undersigned at 609-844-3020.

The USPTO is authorized to charge Deposit Account No. 50-1943 for any charges in connection with this matter.

Respectfully submitted,

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